Solution- and Solid-State Evidence for Alkali Metal Cation−π Interactions with Indole, the Side Chain of Tryptophan

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Cation−π interactions have received considerable attention recently, particularly in the context of biology. The interaction of an aromatic π-system with an alkali metal cation has been known since the pioneering studies of Kebarle and co-workers in 1981.[1] They showed that the interaction (gas phase) between benzene and K^{+} was stronger than a similar interaction with a single water molecule (ΔH = −30 vs −29 kcal/mol). Aromatic π-donor side arms in proteins are known to interact with a few ammonium ions.[2] Theoretical calculations have shown that the aromatic side chains of Phe, Tyr, and particularly the indole side chain of Trp should be potent π-donors for alkali metal cations.[3] It was suggested that π-donor interactions play a role in establishing selectivity in the Shaker potassium channel.[4] This interesting hypothesis was disproved by site-directed mutagenesis[5] and a crystal structure.[6] The postulate, however, increased the general interest in cation−π interactions for which experimental evidence is now being actively sought.

We report experimental confirmation of cation−π interactions between alkali metal ions and the tryptophan side chain, indole. Three of the four solid-state structures presented are of complexes and (1) show unambiguous cation−π contacts with Na^{+} or K^{+}, and (2) demonstrate a preference for the pyrrolo, rather than benzo, subunit in the π-coordination of indole. The solid-state data clearly parallel results obtained for these same complexes in solution.

Compound **1** is a bibracchial (2-armed) lariat ether having the ability to complex alkali metal cations.[7] The crown ether system was chosen because it affords a binding site within the macroring that has previously been characterized for hundreds of cases. The host molecule[8] was designed so that indole was attached in the 3-position as it is in Trp. The 2-carbon spacer chain was selected so that a π-interaction with the ring-bound cation would be optimal with the benzo portion of indole as predicted by computational studies (see below). In many complexes, the
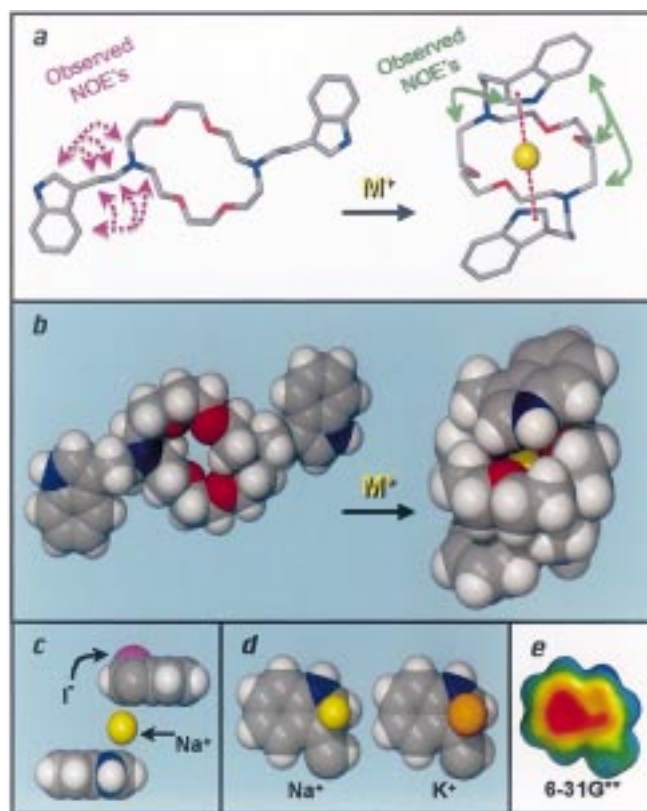
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(8) Compound **1** (mp 129−131 °C, satisfactory analytical data) was prepared by dialkylation of 4,13-diaza-18-crown-6 using 2-(3-indolyl)ethyl bromide by the method reported recently: Schall, O. F.; Gokel, G. W.: *J. Am. Chem. Soc.* **1994**, *116*, 6089−6100.

Figure 1. (a) Tubular model of **1** in the free state (left) and complexed with sodium cation (right). Broken, magenta arrows indicate selected NOE's in **1** and solid, green arrows indicate NOE's in NaI·**1**. (b) CPK rendering of **1** (left) and complexed with Na^{+} (right). (c) Side view of the Na^{+}-indole interaction in NaI·**1**. (d) Top views of cation positions on the indole surface. Top fragment: KI complex; bottom fragment: NaI complex. (e) Electrostatic potential surface of 3-methylindole calculated using 6-31G** (red = negative, blue = positive potential).

counteranion, solvent, or water is present in the cation's solvation sphere.[9] The side arms of **1** are sufficiently flexible that an anion may compete for the bound cation's apical positions.

The structures of **1** alone and complexed with NaI, KI, or KPF$_6$ were obtained by X-ray analysis.
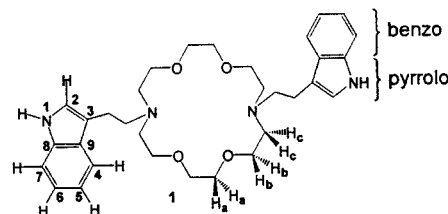
The conformation for **1** in the solid state is typical of 18-membered crowns,[10] and the aromatic side arms are turned away from the macrocycle. Upon complexation, the side arm indoles pack tightly above and below the macroring to fully envelop either Na^{+} or K^{+} (Figure 1a and b). The apical coordination sites of Na^{+} or K^{+} are fully occupied by arene rather than by counteranion or water. A dotted line (Figure 1a) connects the cation with each indole to show the bonding axis between the indole pyrrolo subunits and the cation.

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Table 1. Geometry of the Cation−π Interaction

R	M^+-R distance (Å)		
	NaI	KI	KPF_6
M^+-N(indole)	3.58	3.51	3.57
M^+-C2(indole)	3.23	3.32	3.30
M^+-C3(indole)	3.51	3.57	3.52
M^+-C8(indole)	4.05	3.89	3.98
M^+-C9(indole)	4.02	3.91	3.94
M^+−pyrrolo centroid	3.50	3.45	3.48
M^+−benzo centroid	4.77	4.59	4.67
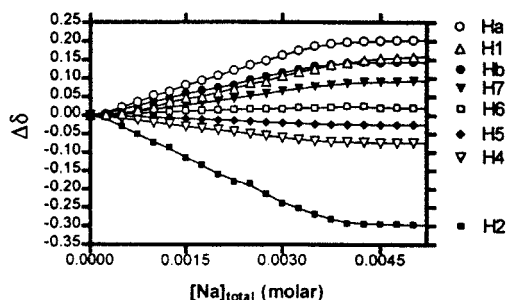
Figure 2. ^1H chemical shift data from titration of 5 mM **1** in CD_3COCD_3 with NaI at 25 °C.

The cation−π interaction of the parallel arenes (Figure 1c) is clearly strong enough to exclude I^-, PF_6^-, acetone, or adventitious H_2O from interaction with the metal cation. The iodide ion shown in Figure 1c is excluded from the first solvation sphere ($Na^+ \leftrightarrow I^-$ = 6.17 Å) and π-bonded directly to the indole nitrogen (N1).

The indole groups occupy virtually identical positions whether the included cation is Na^+ or K^+ and when the anion is I^- or PF_6^-. The exact orientations of Na^+ and K^+ with respect to the indole are shown in a cutaway view (Figure 1d). Selected distances from the solid-state structures are listed in Table 1. Three important structural issues deserve note. First, all distances ($M^+ \cdots N$, $M^+ \cdots O$) and angles (CXC, XCC) in the crown ether portion of the complex are typical.[11] Second, the pyrrolo centroid is closer to the cation by >1 Å in every case than is the benzo centroid (see Table 1). Third, carbon-2 of the pyrrolo subunit is closer than any other atom to the bound cation in all cases examined.

The NaI complex of **1** was studied by ^1H NMR to determine if the solution and solid-state structures correlated. Our data suggest that the structures are identical. A solution of **1** (5 mM in CD_3COCD_3, 25 °C) was titrated with NaI (0.5 M in CD_3COCD_3, Figure 2). The largest observed chemical shift increment was for H2 (■): $\Delta\delta_\infty = -0.30$ ppm. This hydrogen atom is on the carbon atom found closest to the bound cation in every case. The macroring hydrogens [H_a (○), H_b (●)] showed typical downfield shifts upon complexation.[12] The hydrogen on the indole nitrogen [H1 (△)] was also shifted downfield to a comparable degree. Hydrogens on the benzo portion of the indole (H4−H7) exhibited modest shifts (≤0.10 ppm). These chemical shifts are expected to be relatively unaffected by complexation because the solid-state structures show that they are most remote from the cation.

2D NOESY experiments were conducted on **1** ([**1**] = 10 mM in CD_3COCD_3) in the absence and presence of NaI. Arrows show some of the observed cross-peaks in Figure 1a. When no salt is present (magenta, broken arrows), strong NOE cross-peaks are observed between H4 and H2 on the indole and the broad resonance due to the spacer arm hydrogens and the proximate macrocycle methylenes (H_c). In the presence of NaI, the cross-peak between the indole H4 and the crown hydrogens completely

disappears. Cross-peaks were observed between H2 and both H_c and the side chain methylenes in the complex. New cross-peaks between H7 and both H_b and H_c were observed in the complex (green, solid arrows in Figure 1a).

The distances observed for cation arene contacts in the solid state structures are approximately as expected. Ionic radii for Na^+ and K^+ are reported for the 8-coordinate cations to be 1.18 Å and 1.51 Å, respectively.[13] Using an arene thickness value of 3.50 Å, we would expect the Na^+-pyrrole centroid distance to be 1.75 Å + 1.18 Å = 2.93 Å. For the K^+ sandwich complex, the corresponding sum of van der Waals radii is 3.26 Å. The observed values are 3.50 Å and 3.46 ± 0.02 Å for the Na^+ and K^+ complexes, respectively. The reported calculated contact distance (for a Na^+ ion positioned over the pyrrolo subunit of indole)[14] is ∼2.47 Å. Values for the Na^+-centroid distance in various phenyl- or benzo-to-cation contacts were recently reported to lie in the range 2.84−4.95 Å.[15] The three structures reported here are, however, the first definitive examples of Na^+ or K^+ in complexes with an indole ring.[16]

A question posed in several computational studies (all on unsubstituted indole) is whether the pyrrolo or benzo fragment is the preferred π-donor for an alkali metal. These studies conclude that the benzo centroid is the preferred π-binding site. One recent calculation indicates that Na^+ binding by the benzo subunit is favored by ∼4 kcal/mol over that by the pyrrolo fragment.[14] Ab initio calculations of electrostatic potential surface reported for indole show the greatest negative charge density over the benzo ring.[17] For comparison, a calculation was done on 3-methylindole using the methodology previously described.[17] The calculated electronic distribution for 3-methylindole was similar to that of indole (Figure 1e).

The experimental results presented here show that in all three cases, pyrrolo, rather than benzo, proves to be the π-donor. We note that neither Na^+ nor K^+ is aligned precisely with either centroid (Figure 1d). In fact, the closest contact with the alkali metal cation is always C2. Solution studies confirm the structure of one of these complexes, further reinforcing the conclusion that indole, and particularly pyrrolo, is an excellent π-donor for Na^+ and K^+ cations.

The lariat ether model system has permitted us not only to demonstrate cation−π complexation of Na^+ and K^+ with the indole residue, it has allowed experimental discrimination between the two aromatic subunits. Molecular models show that either the benzo or pyrrolo subunit of **1** is sterically accessible to the ring-bound cation, but in all three cases it is the latter that serves as the π-donor. Additional solution- and solid-state studies are underway to further define the interactions of indole, and by extension tryptophan, with biologically relevant alkali and alkaline earth metal ions.

Supporting Information Available: Experimental data for **1** (PDF) and crystal data for **1**, **1**·NaI, **1**·KI, and **1**·KPF_6 in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

JA9907921

(11) Bond distances for the metal ion to σ-donors were as follows for the NaI, KI, and KPF6 complexes respectively: M^+−N(crown, avg) 3.03, 3.06, 2.97; M^+−O(crown, avg) 2.47, 2.70, 2.75.
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(16) Wouters[15] reported that Trp123 in hen egg white lysozyme coordinates a sodium cation. The reported temperature factor is 42.6 Å^2 for the sodium. In other, higher-resolution structures of lysozyme (such as PDB codes 1LSE and 1HEL) there are water molecules assigned in this region (also with high temperature factors). A more conclusive example is from rhodanese where Trp287 is in close contact with a Cs^+ (Kooystra, P. J. U.; Kalk, K. H.; Hol, W. G. J. *Eur. J. Biochem.* **1988**, *177*, 345−349).
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